



Niementowski-type synthesis of pyrido[3,2-*e*][1,2,4]triazines: potent *aza*-analogs of pyrido[2,3-*b*]pyrazine fungicides

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ABSTRACT

Novel trisubstituted pyrido[3,2-*e*][1,2,4]triazines have been found to possess similar biological activity to the corresponding pyridopyrazine fungicides against important phytopathogens such as *Mycosphaerella graminicola* (wheat leaf blotch), *Magnaporthe grisea* (rice blast), and *Rhizoctonia solani* (rice sheath blight). They have been prepared for the first time from a monocyclic triazine by Niementowski-type ring condensation.

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1. Introduction

The pyrido[2,3-*b*]pyrazines are a novel class of experimental fungicides, which are highly active against several different phytopathogens such as *Mycosphaerella graminicola* (wheat leaf blotch), *Puccinia recondita* (wheat brown rust), and *Magnaporthe grisea* (rice blast).¹ Their fungicidal efficacy is due to their ability to promote fungal tubulin polymerization, which leads to a disruption of microtubule dynamics. The same mode of action is also used in the treatment of several cancer diseases with natural products such as taxol and vinca alkaloids, like vinblastine and vincristine.² During the course of our further exploration of this area, we studied the influence of different modifications of the pyridopyrazine scaffold on the fungicidal activity. It turned out that the replacement of one carbon atom in the pyrazine moiety of **1** by nitrogen led to the pyrido[3,2-*e*][1,2,4]triazine **2a** with interesting fungicidal properties (Fig. 1). A literature survey revealed that such special pyridotriazines, which are unsubstituted in the triazine ring and persubstituted in the pyridine moiety, have not been reported so far. Herewith, we describe an efficient procedure for the preparation of pyrido[3,2-*e*][1,2,4]triazines with three substituents in the pyridine ring.

2. Results and discussion

So far, only a few syntheses of pyrido[3,2-*e*][1,2,4]triazines have been published.³ Surprisingly, all these six different publications start from a monocyclic nitro- and hydrazino-substituted pyridine, which is transformed by heteroannulation into a pyridotriazine. This synthesis method did not serve our needs, because our envisaged target molecules with three different substituents in the pyridine moiety of the pyridotriazine would then require penta-substituted pyridine starting materials, which are not readily accessible. Therefore we tried to achieve the pyridotriazine synthesis for the first time from a triazine ring, to which a pyridine ring is

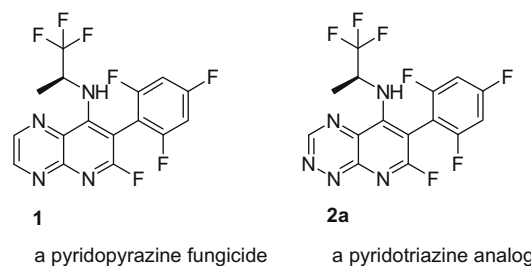


Figure 1. Pyrido[2,3-*b*]pyrazine fungicide **1** and its pyrido[3,2-*e*][1,2,4]triazine analog **2a**.

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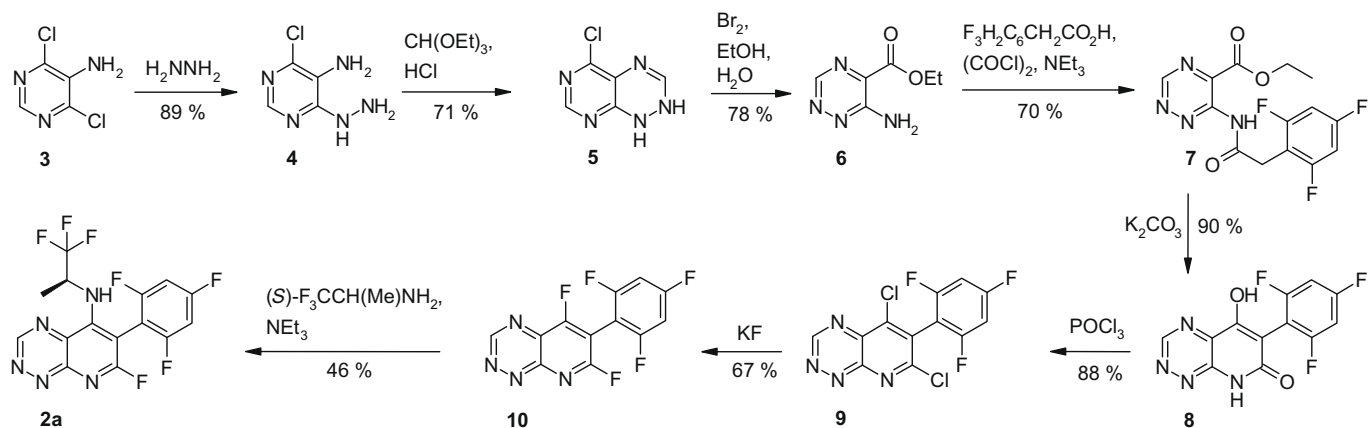
added through a Niementowski-type ring condensation. In the Niementowski reaction^{4,5} a sub-type of the Friedlaender quinoline synthesis,⁶ a 2-amino aryl or heteroaryl acid derivative reacts with an active methylene compound directly to give oxygenated aza-naphthalenes.

The required 6-amino-[1,2,4]triazine-5-carboxylic acid ethyl ester (**6**) was obtained in three steps from commercially available 5-amino-4,6-dichloropyrimidine (**3**) following a literature procedure (Scheme 1).⁷ This 1,2,4-triazine was then converted under Niementowski-type conditions by acylation with 2,4,6-trifluorophenylacetyl chloride and subsequent base-mediated ring closure of the intermediate amide **7** to the dihydroxyprido[3,2-*e*]-as-triazine **8**. According to NMR analysis, the oxygen substituent in position 7 forms a lactam function together with the adjacent ring nitrogen atom. 5-Hydroxy-6-(2,4,6-trifluorophenyl)-8*H*-pyrido[3,2-*e*][1,2,4]triazin-7-one (**8**) was then further transformed with phosphorus oxychloride to the dichloro-derivative **9**, which in turn underwent a halogen exchange reaction with spray-dried potassium fluoride to its difluorinated analog **10**. Finally, the regioselective replacement of the fluoro substituent in position 5 with (*S*)-2,2,2-trifluoroisopropylamine delivered the desired pyrido[3,2-*e*][1,2,4]triazine **2a** with three different substituents in the pyridine moiety (Scheme 1).^{8,9} In our screening, the pyridopyrazine **1** and its pyridotriazine analog **2a** showed similar potency against the fungal plant pathogens *M. graminicola* (wheat leaf blotch), *M. grisea* (rice blast), and *Rhizoctonia solani* (rice sheath blight).

Several other primary and secondary amines could also be introduced into position 5 of the pyrido[3,2-*e*][1,2,4]triazine scaffold (Table 1). With the exception of **2b**, all aminations proceeded either regioselectively or at least predominantly in position 5. In some cases, however, especially with nucleophilic amines, considerable amounts of the diamination products **11a–h** could be isolated, which are devoid of any fungicidal activity.

5,7-Dichloro-6-(2,4,6-trifluorophenyl)-pyrido[3,2-*e*][1,2,4]triazine **9** could be transformed into some novel trisubstituted heterobicyclics, in a similar manner to the monoamination of the difluoro building block **10**. Thus reaction of **9** with a thiolate, such as sodium cyclopentylthiolate, or an alkoxide, such as sodium methylate, leads similar to the monoamination of the corresponding difluoro building block **10**, regioselectively to the introduction of the new substituent into position 5, delivering the sulfide **12** and the ether **13**. The chlorine atom of **13** was exchanged with a cyano group by reaction with sodium cyanide, delivering **15**, and by isopropyl amine, leading to **16**. Both reactions were performed under microwave irradiation.¹⁰ Finally, the reaction of **9** with cyclohexylmagnesium bromide led to the 5-cyclohexyl derivative **14** (Scheme 2).

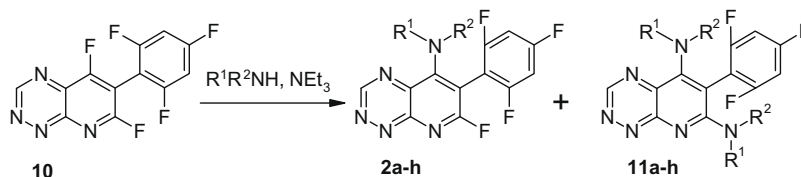
In conclusion, we have achieved the synthesis of the first pyrido[3,2-*e*][1,2,4]triazines with three substituents in the pyridine moiety. In contrast to some earlier published protocols, which all used pyridine starting materials, for the first time this biheterocyclic scaffold was prepared from a monocyclic triazine building block. The halogen atom in position 5 of 5,7-dihalogenated pyrido-



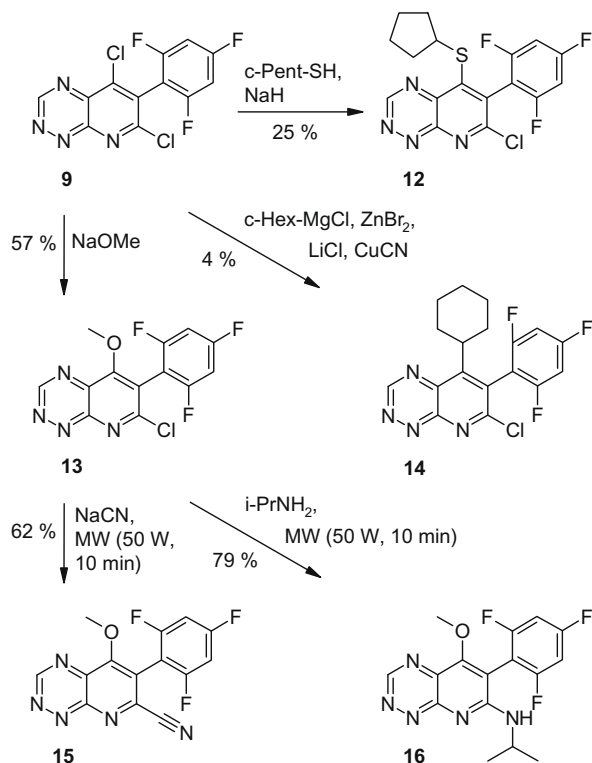
Scheme 1. Synthesis of the trisubstituted pyrido[3,2-*e*][1,2,4]triazine **2a**.

Table 1

Synthesis of pyrido[3,2-*e*][1,2,4]triazines **2a–h** with different amine moieties (all yields and ratios isolated material)



Compound	R ¹	R ²	Yield of 2 (%)	Mp of 2 (°C)	Ratio 2 : 11
2a	(<i>S</i>)-F ₃ C(Me)CH–	H	46	93–94	1:0
2b	Me ₂ CH–	H	18	92–93	1:3
2c	Me ₂ CHCH ₂ –	H	34	128–129	1:1
2d	Et(Me)CH–	H	43	102–104	3:2
2e	Me ₃ C–	H	43	116–118	1:0
2f	–	H	62	121–123	1:0
2g	–CH ₂ CH ₂ CH ₂ –	H	40	153–154	3:1
2h	–CH ₂ CH ₂ CH ₂ CH ₂ –	H	30	136–138	3:1



Scheme 2. Synthesis of the trisubstituted pyrido[3,2-*e*][1,2,4]triazine **2a**.

pyrazines could be regioselectively replaced by amino, alkyl, alkoxy, and alkylthio groups.

References and notes

- Crowley, P. J.; Lamberth, C.; Müller, U.; Wendeborn, S.; Nebel, K.; Williams, J.; Sageot, O.-A.; Carter, N.; Mathie, T.; Kempf, H.-J.; Godwin, J.; Schneiter, P.; Dobler, M. R. *Pest Manag. Sci.* **2010**, *66*, 178–185.
- (a) Zhou, J.; Giannakakou, P. *Curr. Med. Chem. Anticancer Agents* **2005**, *5*, 65–71; (b) Honore, S.; Pasquier, E.; Braguer, D. *Cell Mol. Life Sci.* **2005**, *62*, 3039–3056; (c) Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253–265; (d) Li, Q.; Sham, H. L. *Expert Opin. Ther. Patents* **2002**, *12*, 1663–1702; (e) Jordan, M. A. *Curr. Med. Chem. Anticancer Agents* **2002**, *2*, 1–17.
- (a) Reich, M. F.; Fabio, P. F.; Lee, V. J.; Kuck, N. A.; Testa, R. T. *J. Med. Chem.* **1989**, *32*, 2474–2485; (b) Ple, N.; Queguiner, G.; Pastour, P. *CR Hebd. Seances Acad. Sci., Ser. C* **1976**, *283*, 487–489; (c) Messmer, A.; Gelleri, A.; Benko, P.; Pallos, L. *Magy. Kem. Foly.* **1976**, *82*, 173–179; (d) Benko, P.; Messmer, A.; Gelleri, A.; Pallos, L. *Acta Chim. Acad. Sci. Hung.* **1976**, *90*, 285–299; (e) Gelleri, A.; Messmer, A.; Benko, P.; Pallos, L. *Acta Chim. Acad. Sci. Hung.* **1976**, *90*, 301–311; (f) Lewis, A.; Shepherd, R. G. *J. Heterocycl. Chem.* **1971**, *8*, 41–46.
- Hisano, T. *Org. Prep. Proced. Int.* **1973**, *5*, 145–193.
- For some recent applications of the Niementowski reaction see: (a) Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron* **2003**, *59*, 1413–1419; (b) Alexandre, F.-R.; Berecibar, A.; Besson, T. *Tetrahedron Lett.* **2002**, *43*, 3911–3913; (c) Son, J. K.; Kim, S. I.; Jahng, Y. *Heterocycles* **2001**, *55*, 1981–1986; (d) Domon, L.; Le Coeur, C.; Grelard, A.; Thiery, V.; Besson, T. *Tetrahedron Lett.* **2001**, *42*, 6671–6674; (e) Zhou, Z.-L.; Navratil, J. M.; Cai, S. X.; Whittemore, E. R.; Espitia, S. A.; Hawkinson, J. E.; Tran, M.; Woodward, R. M.; Weber, E.; Keana, J. F. W. *Bioorg. Med. Chem.* **2001**, *9*, 2061–2071.
- (a) Thummel, R. P. *Synlett* **1992**, 1–12; (b) Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37–201.
- Temple, C.; Kussner, C. L.; Montgomery, J. A. *J. Org. Chem.* **1971**, *36*, 2974–2978.
- Crowley, P. J.; Dobler, M.; Müller, U.; Williams, J. WO 2004/056829 (Syngenta); *Chem. Abstr.* **2004**, *141*, 89107.
- Typical synthesis procedure for compound 2:** A solution of 2,4,6-trifluorophenylacetyl chloride (10.5 g, 50 mmol) in 30 ml of dichloromethane is added at 0 °C to a solution of 6-amino-[1,2,4]triazine-5-carboxylic acid ethyl ester⁷ (**6**, 8.5 g, 50 mmol), pyridine (4.0 g, 50 mmol), and catalytic amounts of 4-*N,N*-dimethylaminopyridine in 170 ml of dichloromethane. The resulting suspension is stirred for 16 h at room temperature and then extracted with 2 N hydrochloric acid and water. The organic layer is washed with brine, dried over sodium sulfate, and evaporated. The remainder is purified by chromatography on silica gel, using cyclohexane/ethyl acetate 3:1 as eluent, to give 6-[2-(2,4,6-trifluorophenyl)-acetylamino]-[1,2,4]triazine-5-carboxylic acid ethyl ester (**7**, 12 g, 35 mmol, 70%) as a viscous oil, which solidified. Mp 106–107 °C. ¹H NMR (CDCl₃): δ (ppm) 1.46 (t, 3H, *J* = 7.2 Hz), 4.10 (s, 2H), 4.48 (q, 2H, *J* = 7.2 Hz), 6.73 (t, 2H, *J* = 8.5 Hz), 9.62 (s, 1H), 10.03 (s, 1H). MS *m/z*: 341 (C₁₄H₁₁F₃N₄O₃+H)⁺. A mixture of **7** (6.0 g, 18 mmol) and anhydrous potassium carbonate (3.75 g, 27 mmol) in 50 ml of *N,N*-dimethylformamide is stirred for 2 h at 80 °C. Subsequently the reaction mixture is cooled, poured into water, and acidified to pH 5 with 5 N hydrochloric acid. After extraction with ethyl acetate, the organic layer is dried over sodium sulfate and evaporated to give an orange solid, which was triturated with *tert*-butyl methyl ether to deliver 5-hydroxy-6-(2,4,6-trifluorophenyl)-8H-pyrido[3,2-*e*][1,2,4]triazin-7-one (**8**, 4.7 g, 16 mmol, 90%) as a yellow powder. Mp 170–171 °C. ¹H NMR ((CD₃)₂SO): δ (ppm) 7.29 (t, 2H, *J* = 8.4 Hz), 9.73 (s, 1H), 12.89 (s, 1H). MS *m/z*: 293 (C₁₂H₅F₃N₄O₂-H)⁺. A solution of **8** (4.0 g, 14 mmol) in 20 ml of phosphorus oxychloride was heated to 85 °C for 2 h. The reaction mixture is cooled to 55 °C and the solvent is removed at this temperature in vacuo. The remaining oil is diluted with ethyl acetate and washed with brine and aqueous sodium bicarbonate solution. The organic layer is dried over sodium sulfate and evaporated, the residue is purified by chromatography using cyclohexane/ethyl acetate 3:1 as eluents to deliver 5,7-dichloro-6-(2,4,6-trifluorophenyl)-pyrido[3,2-*e*][1,2,4]triazine (**9**, 3.9 g, 12 mmol, 88%) as reddish solid. Mp 143–144 °C. ¹H NMR (CDCl₃): δ (ppm) 6.96 (t, 2H, *J* = 8.5 Hz), 10.24 (s, 1H). MS *m/z*: 332 (C₁₂H₃Cl₂F₃N₄+H)⁺. A suspension of **9** (2.9 g, 8.7 mmol) and spray-dried potassium fluoride (1.5 g, 26 mmol) in 10 ml of sulfolane is heated to 130 °C for 2 h. The reaction mixture is cooled, poured into water, and extracted with ethyl acetate. The combined organic layer is washed with brine, dried over sodium sulfate, and evaporated. The residue is purified by chromatography using cyclohexane/ethyl acetate 3:1 as eluents to give 5,7-difluoro-6-(2,4,6-trifluorophenyl)-pyrido[3,2-*e*][1,2,4]triazin-5-yl-((*S*)-2,2,2-trifluoroisopropylamine) (**10**, 1.7 g, 5.8 mmol, 67%) as yellow powder. Mp 160–161 °C. ¹H NMR (CDCl₃): δ (ppm) 6.95 (t, 2H, *J* = 8.6 Hz), 10.21 (s, 1H). MS *m/z*: 299 (C₁₂H₃F₅N₄+H)⁺. **10** (0.25 g, 0.83 mmol) is added to a mixture of (*S*)-2,2,2-trifluoroisopropylamine (0.21 g, 1.84 mmol) and catalytic amounts of 4-*N,N*-dimethylaminopyridine in 3 ml of *N,N*-dimethylformamide. The reaction mixture is stirred for 16 h at room temperature, then poured into ethyl acetate, and washed with brine. The organic layer is dried over sodium sulfate and evaporated, the residue is purified by chromatography on silica gel, using cyclohexane/ethyl acetate 3:1 as eluents to deliver [7-fluoro-6-(2,4,6-trifluorophenyl)-pyrido[3,2-*e*][1,2,4]triazin-5-yl]-((*S*)-2,2,2-trifluoro-1-methyl-ethyl)-amine (**2a**, 0.15 g, 0.38 mmol, 46%) as a yellow solid. Mp 93–94 °C. ¹H NMR (CDCl₃): δ (ppm) 1.45 (d, 3H, *J* = 7.0 Hz), 4.21 (dt, 1H, *J* = 9.2 Hz), 6.83–6.98 (m, 2H), 9.96 (s, 1H). MS *m/z*: 392 (C₁₅H₈F₇N₅+H)⁺.
- (a) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; (b) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005; (c) *Microwave Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell Scientific: Oxford, 2005.